CRIA UPDATE
COMMUNITY RESEARCH INITIATIVE ON AIDS VOL. 10 NO. 3

Taking the Pulse of AIDS Research

contents

The Summer 2001 issue of *CRIA Update* takes a look at the direction of AIDS research – where we've been, where we are and where we're going. We've invited a diverse group of researchers, clinicians and community members from varying disciplines, experience and backgrounds to offer their perspectives on the current state of AIDS research. Our goal was to create a mosaic of commentaries, to raise provocative questions and entice our readers to think critically about HIV research and the role we all play in setting the agenda.

We asked people to identify what are, in their opinion, the most important areas of research now underway, where the holes in research lie, what important areas of study are languishing and deserving of more attention, what questions are being ignored and what directions research should take in the future. What follows are their (relatively) unedited responses. We deeply appreciate the efforts of the individuals who contributed commentaries for this issue as well as the many others whose time, energy and commitment have been essential to the advances in HIV treatment over the years.

CRIA was originally founded to conduct clinical research based on the immediate needs of the HIV/AIDS community – community in the broad sense of the word. The goal was, and still is, to design research protocols according to those needs. CRIA has grown over the years, particularly with the development of a vibrant treatment education program that complements our work in clinical research. Our commitment to listening to and acting on community concerns remains intact and our mission clear: *CRIA is an independent, non-profit community-based organization committed to improving the length and quality of life for people living with HIV/AIDS through clinical research and treatment education.*

While our commitment and our mission are clear and unwavering, our research agenda is always changing to meet current needs. We continue to welcome community initiatives and have recently completed two studies that were suggested by members of our community, including one that demonstrated the efficacy of topical aspirin in relieving the pain of HIV peripheral neuropathy. We continue to look for pharmaceutical industry sponsored drug trials that offer possibly important advances to members of our community such as our current study of human growth hormone for HIV-related fat redistribution. The increasing prevalence of lipodystrophy and the potentially disabling consequences of this syndrome prompted our interest in this study. In the same area, we're involved in studies that look at the effect of different combinations of antiretrovirals on carbohydrate metabolism.

The interest of patients on HAART in trying treatment interruptions to reduce the burden of side effects as well as other problems associated with daily HAART led to our working with a pharmaceutical company to develop a protocol that takes another look at Ampligen, this time to see if its use can prolong the periods of treatment interruption by keeping viral loads undetectable longer than without Ampligen.

The use of complementary and alternative therapies is widespread in our community, and their role and advantages deserve examining. We've developed a study that will help us to understand the role of these integrative therapies in the clinical care of people living with HIV. We hope to build on the findings of this initial work and plan to develop clinical programs that will evaluate specific alternative medicine interventions.

(*continued on page 14*)

SUMMER 2001

CRIA UPDATE

Editor in Chief
J Daniel Stricker

Editor
James Learned

Medical Editor
Jerome A. Ernst, MD

Publications Manager
Mark Milano

CRIA is an independent, non-profit, community-based AIDS research and treatment education organization dedicated to rapidly improving the length and quality of life for people living with HIV/AIDS. CRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of *CRIA Update* are available free to agencies that provide services to people living with HIV/AIDS. For more information, call Judy Codrington at 212-924-3934 ext. 121.

CRIA
230 West 38th St., 17th Floor
New York, NY 10018
Phone: (212) 924-3934
FAX: (212) 924-3936
Internet address: www.criany.org

TRIALS CURRENTLY ENROLLING

Serostim® for HARS

CRIA has begun enrollment on this multicenter study that follows-up on a national level a previous pilot study that CRIA sponsored and conducted. This current 26-week, double-blind, randomized, placebo-controlled study looks at the effectiveness and safety of Serostim“ (human growth hormone) when used to treat the abnormal fat distribution that occurs in patients treated with antiviral drugs for HIV infection. Patients with the condition know as HARS (HIV-related adipose redistribution syndrome) often have increased amounts of fat in the abdomen, the upper back, and (especially in women) in the breasts. If you are an adult who is HIV+, are on a stable anti-HIV drug regimen, and have problems with abnormal fat distribution, you may be eligible for the study.

Vigilance II Genotyping Study

The purpose of this study is to determine if an HIV-1 RNA genotype report is effective and safe to use for choosing therapy for HIV infection. We will be gathering data regarding an experimental test called genotyping, in this case the TruGene® HIV-1 Assay, developed by Visible Genetics Inc. Genotyping may allow doctors to see which drugs may or may not work against HIV infection. It may tell you if HIV may be resistant to certain drugs. Resistance means that the drugs given to you for your HIV may not work as well as thought. Genotyping is still being studied as an aid in treating HIV infection.

You may be eligible for this study if: 1. you are an HIV-1 infected person with a viral load of greater than or equal to 1,000 copies/mL 2. you and your doctor have determined that a change in your anti-HIV therapy is indicated; or if no prior therapy has been given for HIV-1, then you and your doctor agree that therapy needs to be started.

You will come in for one blood draw specifically for the study. This blood will be used for the genotyping test. Your personal doctor will get the results of the genotyping test within 7-10 business days and use these results to help choose a drug regimen that may be beneficial to you. We will gather data about your progress (up to one year) from later blood draws by your personal doctor that are part of your regular care. You will be paid $15 after enrolling into the study to cover transportation, lost time from work, or meals. Your insurance company or a state health insurance agency will be billed for the blood tests. If you do not have insurance or state coverage and if you cannot pay for the tests, your study doctor will try to enroll you in a special patient assistance program.

For more information on these studies, please call
Dr. Douglas Mendez at (212) 924-3934, ext. 126
or visit our Web site:
www.criany.org

Editor's Notes

• All material in CRIA Update is presented for educational and informational purposes only, and is not intended as medical advice. All decisions regarding one's personal treatment and therapy choices should be made in consultation with a physician.
• CRIA Update refers to all drugs by both their commercial and scientific names upon their first reference in an article. Thereafter in the article, they will be identified with the name by which we feel they are most commonly known, either commercial or scientific.

A Long Road Traveled: Conflicts, Community and Clinical Trials

by Richard Jefferys

The historical record of progress in AIDS research lies not only in the medical literature, but also in the community-produced clinical trial directories that have tracked experimental protocols as they opened and closed over the years. Studies of failed treatments generally don't get published, and many of yesterday's therapeutic hopefuls have faded from the collective memory. Pick up an old clinical trial directory, however, and you can find the entry criteria for a "tat inhibitor" study that people once traveled across the US to try and join. The directories also reflect the effects of increasing community involvement in designing research protocols, such as increased study of opportunistic infection treatments, less restrictive entry criteria and greater attention to protecting the interests of trial participants. The very creation of the publications reflected a thirst for information about experimental treatments that most scientific investigators had never previously experienced.

"To rely solely on official institutions for our information is a form of suicide," wrote John S. James in the May 9, 1986 issue of his groundbreaking San Francisco-based newsletter, AIDS Treatment News.

Looking back over two decades of trials, important themes emerge that continue to sound in current debates about the direction of HIV/AIDS research. Most prominently, the agendas of the various stakeholders – people with HIV/AIDS, the pharmaceutical industry, the government and the scientists – have regularly collided, with the outcome often decided by who wielded the most money and political power rather than the logic of a given position. Unsurprisingly, it was people with HIV/AIDS and their advocates who had to battle hardest to be heard and, despite significant victories, this remains the case today.

Find a Bug, Find a Drug:
AZT With Everything (1987-89)

The identification of HIV in 1983 prompted a hunt for an antiretroviral magic bullet that one activist characterized as "find a bug, find a drug." But people with AIDS were dying from infections such as *pneumocystis carinii* pneumonia, or PCP, that could potentially be treated with older off-patent drugs that the brand name pharmaceutical industry – and the researchers that relied on them for funding – had little interest in studying.

The saga of aerosolized pentamidine starkly illustrates the point. Pentamidine, an old antiparasitic treatment, was known to have activity against PCP but, for optimal preventive use, it had to be inhaled using a nebulizer, a device used for asthma treatments. Although some doctors began using the drug for PCP prevention, insurers would typically not reimburse for it due to the lack of official FDA approval. The urgent need for a clinical trial turned attention to the newly established, government-sponsored AIDS Clinical Trials Group (ACTG), which was set up to address such critical research questions. The ACTG, however, appeared to inherit from the government an ability to take a simple task and, assisted by endless committee discussions, transform it into an unassailable morass of confusion and complexity.

"the direction of research...has often been decided by who wielded the most money and political power rather than logic..."

Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) and thus ultimate head of the ACTG, went as far as telling activists attending a 1987 meeting that there was no data to suggest PCP prophylaxis was beneficial and that it may, in fact, be dangerous. While the ACTG continued to agonize over exactly how a pentamidine trial should be conducted, the HIV/AIDS community stepped in to fill the void. The then newly established CRI in New York, headed up by Dr. Joseph Sonnabend, worked with their counterparts in San Francisco to initiate and complete an independent study which led to the approval of aerosolized pentamidine for PCP prevention in 1989. Subsequent studies would confirm the survival benefit associated with this relatively simple intervention.

The ACTG appeared more efficient when it came to setting up trials of anti-HIV drugs. AZT was approved in 1987 based on evidence of a short-term survival benefit in people with advanced disease (a previous episode of PCP or T-cells less than 200), but the ACTG rushed to implement studies that might expand the drug's use to people who hadn't yet developed symptoms. A few ACTG-affiliated researchers, seemingly whipped into a froth of therapeutic euphoria by AZT's arrival, advocated early use of the drug without any supporting evidence whatsoever. Many people living with AIDS had reason to be less enthusiastic about the drug, particularly those whose nights were interrupted by clanging alarms reminding them to take their next every-four-hours AZT dose (the horrifying schedule for the equally horrifying 1,500 mg daily dose used at the time).

A Seat at the Table (1990-93)

"The companies who want their profits, the bureaucrats who want their turf, and the doctors who want to avoid making waves have all been at the table. The persons with AIDS who want their lives must be there, too." - John S. James, AIDS Treatment News, May 9, 1986.

Frustration with the ACTG's monomaniacal approach led to a legendary protest in May 1990, when over a thousand activists stormed the campus at the National Institutes of Health demanding a seat at the table. Anthony Fauci, always the consummate politician, calmed the situation by inviting a few

(continued on next page)

(continued from page 3)
protesters into his office for a meeting. The end result was the birth of the ACTG's Community Constituency Group (CCG).

The CCG included more than 30 activists who distributed themselves across each of the various committees of the ACTG, including the executive committee. Imperfect as the system may have been, there is evidence in clinical trial directories of the era that the community input was valuable. For example, there were 13 ACTG trials of opportunistic infection treatments in the New York State directory published by AIDS Treatment Resources in the winter of 1990. By winter '93, the number had expanded to 21, and two trials were specifically studying treatments for opportunistic infections in women.

Attempts to involve a wider community also led to the opening of a second Federally-sponsored clinical trials network, the Terry Beirn Community Program for Clinical Research on AIDS (CPCRA). Terry Beirn was a dedicated activist who served as managing editor of the first national HIV clinical trials directories published by the American Foundation for AIDS Research (amfAR). While the ACTG studies were conducted at academic centers around the US, the CPCRA included community-based clinics with the aim of involving a more representative and diverse population of people with HIV. The approval of drugs studied primarily in gay white men (while partly a testament to initial activism and altruism on their part) represents not only a political but also a critical scientific issue for women and communities of color, and it was hoped that the CPCRA would help address the problem. Today, the CPCRA is having to fight for its existence, demonstrating that the lack of diversity in trials remains another of the recurring, unresolved themes of HIV/AIDS research.

The sad coda for this period was the 1993 International AIDS Conference in Berlin. The ill-founded enthusiasm for early AZT treatment crashed and burned with the results of the Concorde study, which showed no survival benefit and a hint of just the opposite, wreaking psychic havoc on people with HIV but apparently leaving the researchers that had advocated the approach unscathed.

Protease Inhibited (1994-1996)

The first protease inhibitor crept into human safety trials in 1991. By 1994, Ro 31-8959, now known as saquinavir, had made it as far as an ACTG Phase II/III study (dubbed ACTG 229). In getting there, however, saquinavir provided a lesson in the limitations of community input into the ACTG process. On September 30, 1992, CCG representative Mark Harrington wrote a polite but concerned letter to principal investigator Ann Collier about the slated trial:

"I remain perplexed about the current design of ACTG 229. In particular, I share the CTRC's (Clinical Trials Review Committee) concern about 'the selection of 600 mg tid [three times a day] as the dose of Ro 31-8959 [saquinavir] since there is no established maximum tolerated dose.' Doses as high as 1200-1800 mg tid have been tested in HIV-negative patients and found to be safe... but people with HIV have only been given doses up to 600 mg tid. I would concur with the CTRC that 'the need for the pharmaceutical sponsor to be forthcoming with data from their European trials' is pressing as we proceed towards opening ACTG 229."

The dose selected by the ACTG was (surprise!) 600 mg tid. The fallout from this decision was profound. The final results of the study, employing a new technique called PCR to measure the amount of HIV's genetic material in the blood (the now familiar viral load test) revealed a slightly better reduction in people taking saquinavir combined with AZT and ddC (Hivid) compared to the double combination of AZT and ddC. A similar incremental benefit in T-cell count increases was also observed. But, due to the low dose of saquinavir, the effects were short-lived. Yet worse, many trial participants developed resistance to the drug that would turn out to blunt the effect of newer protease inhibitors which, although no more potent against HIV in the test tube, were being given at doses that led to dramatically better viral suppression and immunologic recovery. Had Harrington's warning been heeded, this disaster could have been avoided. A high-dose saquinavir study eventually confirmed what the CTRC suspected: antiviral activity was dramatically enhanced without significant additional toxicity.

Thankfully, 1995 saw more impressive results from studies of saquinavir's protease inhibiting brethren, ritonavir (Norvir) and indinavir (Crixivan). Combining a protease inhibitor with two nucleoside analogues was shown to lead to prolonged suppression of HIV replication and a surprising rebound in T-cell counts and functional immunity. Although low-dose saquinavir was eventually approved in December '95, the more effective drugs followed rapidly on its heels, receiving approval in March '96. These events followed two studies showing a survival benefit (and a correlation between survival and viral load reduction) with dual nucleoside therapy, lending credibility to the notion that the addition of a protease inhibitor would further prolong life. The 1996 International AIDS Conference in Vancouver launched the idea of these triple combinations into the public imagination, inaugurating the era of Highly Active AntiRetroviral Therapy (HAART).

HAART Realities (1997-2000)

At the community level, it rapidly became apparent that HAART could produce remarkable health rebounds in people with symptomatic disease and AIDS. The drugs did not work for everyone, but the advantages over single and dual nucleoside treatments were abundantly clear. The availability of HAART altered the research landscape by finally making more effective treatment available outside of clinical trials. Efforts to compare regimens continued and added two nucleoside analogues plus a non–nucleoside (NNRTI) drug to the HAART roster, but the past few years are perhaps best characterized by the trials that either didn't happen or were achingly slow to get started.

Most notably, the key question of when it is best to begin HAART treatment has gone unanswered to this day. In a woeful bout of collective amnesia, many of the same researchers that championed

(continued on page 12)

Guy Pujol

Executive Director, AIDS Treatment Initiatives, Atlanta, Georgia

"Treatment is not a science. It is an art."

I use this phrase almost daily as I discuss treatment strategies with people considering their options. We have to understand that there is not one medication or one combination which will work for everyone. Many factors go into determining a first, second, or subsequent regimen. Side effects, food restrictions, and convenience factors all add to the complexity of the decision. And that is just the beginning of the growing complexities of treatment. Resistance, cross resistance, drug-drug interactions and a host of other issues complicate the process even more.

When I attend International AIDS Society symposia, I am constantly amazed at the diversity of opinions regarding treatment strategies held by doctors participating in the discussion. In one part of the symposia, a patient case study is presented to the participants. After the patient's medical history is presented, the doctors in the room vote on which combination they would recommend prescribing next. Using a keypad like the audience uses on "Who Wants to be a Millionaire?" the participants select regimen A, B, C, D, or E. Then the results are projected on a screen for everyone to see. One would hope to see a consensus of opinion or at least a majority favoring one option over the others. But each option often receives approximately the same number of votes. This demonstrates that each doctor considers her or his own set of factors when selecting treatment options—either different regimens or even whether to treat at all.

In light of this diversity, I believe future research needs to examine the issue of treatment strategy itself more closely. Yes, we need to continue researching new and novel treatments such as fusion inhibitors, integrase inhibitors, and nucleotide reverse transcriptase inhibitors. Personally, I am encouraged by these new classes of drugs that stop viral replication earlier in HIV's life cycle, allowing the T-cell to remain viable (unlike protease inhibitors). However, I think research needs to take a more comprehensive approach to disease management than just attacking the virus.

We are over–treating the virus and under–treating the person. More attention needs to be given to therapies that strengthen the immune system and allow the body's natural defenses to aid in viral suppression. The new generation of antiretrovirals with easier dosing schedules and reportedly fewer side effects is exciting; but they should not be the sole focus of research.

We need more evidence-based studies of the efficacy, advantages, and disadvantages of specific combinations of therapies. For example, long-term side effect studies should not be conducted independent of pharmacokinetic-enhanced regimen studies. New antiretroviral agents should not be studied independent of immune-based therapies and therapeutic vaccines. Studies must begin looking at the potential benefits (and the potential risks) of the next era of combination therapy—that is, combining antiretrovirals, immune-based therapies, and therapeutic vaccines as an integrative approach to disease management.

The science of treatment and research has been too narrowly focused. Maybe a more artistic approach is needed after all. With art, we do not look at each color or line independent of the other colors and lines on the canvas. We look at everything in order to see the big picture. I am convinced we need to do the same as we look at the treatment of HIV.

Kathryn Anastos, MD

Medical Director, Lincoln Medical and Mental Health Center, Bronx, NY;
Principal Investigator, Bronx/NYC consortium, Women's Interagency HIV Study

It is critically important that we expand the research activities in HIV and AIDS to include more women and individuals of color, who now represent 67% of newly diagnosed AIDS cases, 62% of individuals living with AIDS, and 69% of newly reported HIV infections. In the United States, the highest rates of AIDS incidence, HIV prevalence and HIV-related mortality are in black women and men.

There is a growing body of evidence that there are gender and ethnic differences in the laboratory markers we use to advise patients as to disease progression and when to begin HAART. Several investigators have shown that individuals of color and women have lower viral loads than men at early and moderate stages of disease, and a recent study reported that women developed AIDS at a much lower viral load than men: 17,149 copies/ml in women compared to 77,800 copies/ml in men. Other investigators have found that women progress to AIDS or death at higher T-cell counts than men.

These findings are disturbing: most of the HIV infected individuals in the US are women or people of color, and we are lacking adequate information about the prognostic value of our major markers for disease progression. However, because treatment is so effective, and everyone with HIV infection should have access to treatment, the most important question is whether there are differences by gender or race in response to treatment with HAART. While it is clear that HAART is effective in women and people of color, we have not defined the best time for starting therapy, which may be at lower viral loads than the current guidelines suggest. There do exist cohort studies of HIV-positive women

(continued on next page)

(continued from page 5)
which will help us answer these questions for women. However, there is no large enough group being studied to yield these answers for men of color. This needs to be rectified either by enrollment of men of color into clinical trials or by establishment of a cohort study of men of color.

The research needs for women and men of color also include defining the toxic effects of HAART: diabetes mellitus, insulin resistance, osteoporosis and possibly hypertension. These conditions are already more prevalent and cause more health problems (heart attacks, strokes) in women and in communities of color. Thus, it is extremely important that we investigate these side effects of HAART in the communities with the highest rates of HIV infection and already high rates of diabetes and hypertension, the major risk factors for cardiovascular disease, which is the leading cause of death for women and men of color over the age of 45 years.

The ability to delay or prevent HIV disease progression is one of the greatest public health achievements ever. There are precious few chronic diseases in which we are as successful with treatment: 80% decrease in the rates of AIDS and death since 1995. Our treatment regimens are becoming simpler and more tolerable. However, those communities bearing the greatest burden of disease are also those for whom we have the least information regarding the best treatment. While we continue to improve access to treatment for these groups, we also need to improve markedly their access to research programs, so that we advance our scientific understanding of their response to treatment, both in terms of disease progression and rates of side effects.

Craig Wilson, MD

University of Alabama at Birmingham, Departments of Pediatrics and Medicine, Chair of the Adolescent Medicine Trials Network for HIV/AIDS Interventions

HIV-infected adolescents present many management challenges but also a few unique opportunities for directed interventions. Identifying youth infected with HIV through risk behaviors is a particular challenge since many of these youth do not identify the risk behavors with acquiring HIV. Once in care, the challenges of managing HIV-infected adolescents on complex regimens, as well as issues of disclosure and confidentiality, are only made more complex by their age, quite often disrupted traditional social supports and other psychosocial conditions.

One of the most intriguing and under-appreciated areas of inquiry relates to the nature and extent of immune resiliency in adolescents and to what degree it can be used to therapeutic advantage in vaccine-based prevention as well as clinical management of HIV infection. Recent observational data from the Adolescent Medicine HIV/AIDS Research Network have demonstrated that youth, HIV-infected as teens, exhibit increased naïve CD8+ T lymphocytes at all stages of HIV disease compared to HIV-infected adults, and they display relatively normal levels of naïve CD4+ T lymphocytes when compared to uninfected controls. These findings suggest that HIV-infected adolescents may maintain (and have the potential to repopulate) naïve CD4+T lymphocytes to a greater degree than adults owing to persistent thymic function. These findings also suggest HIV-infected adolescents have an increased potential to respond to therapeutic vaccines. It is time to employ a structured treatment interruption strategy interspersed with immune-based therapeutic challenge in recently-infected youth to determine the potential for immune recovery and control of viral replication.

"HIV-infected adolescents may have an increased potential to respond to therapeutic vaccines."

Ongoing studies of the Adolescent Medicine HIV/AIDS Research Network in minority youth will substantially expand our knowledge about responses to HIV proteins and be informative for vaccine development for minority populations. Since adolescents will ultimately be a primary target for preventive vaccination, it is imperative that the enrollment of HIV negative adolescents be accommodated in every efficacy trial of vaccine candidates.

In addition, researching and promulgating effective, multifaceted, and consistent primary prevention programs and messages directed at youth will be an ongoing need for years to come. The newly-funded Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) will be pursuing these objectives in collaboration with existing research networks.

HIV/AIDS Clinical Trials: A Directory for New York State

A comprehensive guide to HIV/AIDS research in New York, New Jersey, Connecticut and Philadelpia. Designed for people with HIV and their care providers. Free to NYS residents and AIDS service organizations.
Call Mark Milano at (212) 924-3934, x123 or write:
CRIA, 230 W. 38th St., 17th floor, NY, NY 10018

Anna Forbes, MS Global Campaign for Microbicides

What's closer to fruition than a vaccine, less elusive than a cure and one of the least discussed avenues of AIDS research? Microbicides!

Efforts to develop topical products that can be used vaginally or rectally to reduce risk of infection with HIV and other STDs have expanded in the last few years – but have drawn little public attention and even less financial support.

Those working in the field agree that, with sufficient political will and investment, an effective microbicide could be developed within five years. About 50 candidate products (excluding Nonoxynol-9) have been identified so far, with the potential of being effective against a range of sexually transmitted infections and all strains of HIV. Four are now being readied for expanded (Phase II/III) safety and efficacy trials that will measure their effectiveness at preventing HIV infection during intercourse.

Inexpensive to produce and distribute, the new microbicides will come in forms familiar to most users, including gels, creams, suppositories and lubricants. Some may be designed for use in conjunction with devices such as a sponge or vaginal ring.

Some will provide protection by blocking or killing the pathogens directly while others, derived from existing antiretroviral drugs, may work by preventing viral replication in the vagina or rectum. Some are based on existing products used in new ways or new combinations; others are based on completely new compounds.

Despite burgeoning scientific promise and overwhelming public health need, investment in microbicide research has been woefully inadequate. Large pharmaceutical companies—the normal engines of product development—have yet to invest because of concerns that products designed to be sold worldwide at low cost will not be profitable enough to recoup the cost of developing them.

The task of microbicide research and development (R&D), therefore, has fallen to non-profit entities, academic researchers, and small bio-pharmaceutical companies, all of which are dependent on government and foundation grants to pursue their research. At present, the NIH invests about 1% of its AIDS-related research budget ($34 million annually) in microbicide R&D. This is supplemented by a modest amount from venture capitalists and private foundations.

Private and public monies for microbicide R&D must expand dramatically. This summer, Congresswoman Connie Morella (R-MD) will introduce the Microbicides Development Act, legislation designed to increase the level of federal investment in microbicide research sufficiently to unblock the research pipeline and assure that promising candidate products don't continue to sit, untested, on laboratory shelves.

Scientists now predict that it will take more than a decade to develop even a partially protective vaccine. With adequate investment, a microbicide could be available in half that time. Over half of all Africans living with HIV/AIDS are women. New infection rates among women are soaring worldwide. Surely these facts make it painfully obvious that receptive sex partners need a way of protecting themselves that they can control. Surely, its worth more than a penny out of every AIDS research dollar to make microbicides happen.

Denise Goodman Member of CRIA's Community Advisory Board

"A heart at peace gives life to the body."

This proverb succinctly expresses what I consider to be the most promising direction for AIDS research. In essence, a lot has been learned through HIV research about the immune system and how to control its deterioration. Going forward, the challenge is to learn to work with the immune system to strengthen and restore life to the body.

The field of immune restoration looks at what drugs and/or substances (natural or engineered) can induce a positive immune response that may prevent or lessen the severity of disease. Maybe this excites me most because I am not a scientist. I'd like to believe that our bodies' natural defense system could be the major player in keeping us healthy and alive.

Immune restoration goes hand in hand with the future of AIDS research – the goal of finding an effective (preventive and therapeutic) HIV vaccine and microbicide. Research is underway to find a vaccine that will induce the immune system to mount an antibody and cellular response to HIV exposure or re-exposure. Our bodies can be a partner in the fight – not just a "consumer".

I find this so exciting, promising, and empowering. That is why I work at Project Achieve. As the Community Relations Coordinator, I seek out interested individuals, agencies and anybody who'll listen, to learn more about vaccine and microbicide research being conducted in New York City and around the world through the HIV Vaccine Trials Network and HIV Prevention Trials Network.

The good news is that the field is intensifying. There are several promising vaccine and microbicide products in pre-clinical and clinical trials today. However, the supply of products and funding to do the research fall far below the urgency with which we need these products. Perhaps this stems from the reality that the

(continued on next page)

Jay A. Levy, MD

Professor of Medicine, University of California, San Francisco

When AIDS was first recognized in the United States 20 years ago, no one expected to see the worldwide spread and devastating effects the virus has had on human populations. For researchers directing efforts at finding ways of controlling HIV infection, the challenge is to provide a solution that can be available for both industrialized and developing countries. One of the major promising approaches toward this objective is eliciting immunologic responses against HIV. This host reaction to the virus is the mechanism by which some individuals have survived this infection for over 20 years without the use of antiviral drugs. These long-term survivors have inherited a natural means for warding off HIV and preventing its destruction of the immune system. We need to discover the secret to this long-term survival and develop strategies for reproducing it in other infected people.

"If the anti-HIV immune response can be restored... antiviral drugs could be stopped or intermittently given."

In particular, information on the proper functioning of both the innate (natural) and the adaptive immune response of HIV will be useful in finding new approaches for future therapies. The current highly active antiviral drugs are very effective in lowering the viral load and reversing the clinical symptoms of HIV infection. However, their long-term effect is limited and a restoration in immunologic responses to HIV has not been achieved. Combining the drugs with immune system activators such as viral protein immunizations and/or immune enhancing cytokines (such as IL-2) would appear to be the best future direction for long-term control of HIV infection. If the anti-HIV immune response can be restored, the potentially toxic antiviral drugs could be stopped or intermittently given. Our own laboratory is pursuing the identification of a novel anti-HIV protein produced by CD8+ cells. This CD8+ cell antiviral factor (CAF) blocks HIV after it enters the cell and prevents its production of progeny viruses. CAF production correlates with a long-term healthy state. Once its nature is known, CAF could be very helpful in therapeutic approaches to HIV infection.

Another topic meriting attention is the evolution of new HIV strains. With the inability to arrest the rapid spread of HIV in certain parts of the world, new types of HIV strains will be emerging. Many of these will represent genetic combinations of two or even three different viral types. These recombinant viruses could pose new problems for antiviral therapies and a vaccine. Recognition of these agents and approaches to control them should be another major emphasis in future research.

Alessandro Di Rocco, MD

Associate Professor of Neurology, Albert Einstein College of Medicine and Beth Israel Medical Center

Neurologic problems remain common in the course of HIV infection, although the introduction of HAART has greatly diminished the frequency and severity of these complications.

Dementia is now much less frequent even in individuals with severe immunodeficiency. The use of AZT first and then of the other antiretroviral medications has diminished the virus load within the brain, limiting the direct infection of brain cells and the indirect toxic effect of viral particles or abnormal immune response that can lead to brain damage. Although the mechanism causing brain cell death is still unknown, it is known that the higher the viral load inside the brain, the more likely an individual is to develop dementia. Most of the drugs currently used, however, have only limited access to the brain. Current research is trying to identify new antiretrovirals that have high efficacy in the brain. Additional research is aimed at understanding how the virus leads to nerve cell damage and at developing treatment that would prevent and stop the premature death of brain cells. Clinical trials will start in the next few months to test the safety and the efficacy of these new drugs.

Neuropathy is another common complication of HIV infection. While neuropathy can be the direct result of HIV infection, it may also be due to some of the antiretroviral drugs, in particular d4T (Zerit), ddI (Videx) and ddC (Hivid). These drugs may, however, be necessary to suppress the viral load and may ultimately help to diminish the rate of neurological complications. Currently there is only treatment for the symptoms of the neuropathy with a number of medications that diminish the burning sensation at the bottom of the feet. There is, however, no therapy that can eliminate the damage to the nerves and cure the neuropathy. A large study with Nerve Growth factor (NGF), a chemical that in laboratory promotes the growth of nerve endings, did not lead to any significant benefit. Current research is looking at whether mitochondria, the particles that produce energy within the nerve cells, are

Denise Goodman *(continued from page 7)*

primary market for these products is the developing world, which has little to no resources to pay for these prevention tools. Locally, we also could use these products. But the voice of the at-risk and infected activist community is notably quite soft. Twenty years of this epidemic has taught us many things, including that low demand equals low supply equals little progress.

Label me a dreamer, but I still believe that, as a community, we

responsible for the neuropathy and at developing new treatments that would cause the re-growth of nerve endings.

Myelopathy is a spinal cord disease that is rather common in HIV infection. As myelopathy progresses very slowly, it is often misdiagnosed or ignored. The symptoms are urgency to urinate, frequent urination, weakness in the legs (often evident when climbing stairs), leg stiffness and sexual dysfunction in men. Myelopathy is not due to viral infection of the spinal cord, but to a metabolic dysfunction induced by the virus that leads to the detachment of the protecting layering (myelin) from the nervous fibers. Current research is trying to determine how the virus causes the metabolic abnormality. Supplementation with the natural amino acid L-methionine has been reported to improve the myelopathy, and this treatment is currently being tested in a larger study. Other therapies are also being studied that could prevent and, possibly, cure the myelopathy.

Neurologic opportunistic infections such as cryptoccocal meningitis, CMV, toxoplasmosis, PML (Progressive Multifocal Leukoencephalopathy) and tumors like lymphoma have become rarer, and better treatment has been developed to treat them.

must and will rally to demand and give input to HIV vaccine and microbicide research. Within a decade I'd like to see the development of at least one HIV microbicide that's available worldwide, easy-to-use, inexpensive, non-contraceptive and erotic. Within two decades, I'd like to see the licensing of an HIV vaccine that's available worldwide, inexpensive, and accepted by the masses.

Tim Horn *Treatment advocate and educator in New York*

Reading through the volumes of research reports generated over the last five years, one could be forgiven for reaching a rather grim conclusion: that clinical research has been more about HIV itself than about how best to treat people who are infected with the virus. Even with the twilight of the eradication hypothesis, the research agenda is unrelenting in its obsession: How soon should we start therapy to hit the virus? How many drugs should we use to push it to undetectable levels? How long can we maintain control over HIV's wily behavior? *Faster. Harder. Longer.* Yet, while there is much to be said for the virus hunters and their medical machismo, HIV remains one of the most aggressively treated diseases known to man for which there is no chance of a cure.

"Clinical research has been more about HIV itself than about how best to treat people who are infected with the virus."

Figuring out today's top research priorities requires that we ask ourselves a much larger question—to what extent do our efforts to battle this virus actually translate into truly feasible health care? For example, it is still not entirely clear when therapy should be initiated. After all, the potential benefit of early therapy is still theoretical, whereas the possibility of long-term side effects is very real indeed. Instead of controlled clinical trials—not a single study has actually been conducted to determine the best time for people to start therapy—researchers have drawn upon a hodgepodge of laboratory and observational studies to contend 'the earlier, the better.' Only well-designed studies will actually tell if someone who starts therapy with a CD4+ cell count of 500 actually does better in the long run than someone who waits until their CD4+ cell count falls to 200.

The issue of when to initiate therapy is only the tip of the iceberg. For every one person currently contemplating when to start treatment, there are nine others who are already up to their ears in triple-drug therapy. What is the best option for people who show signs of drug resistance? The majority of researchers, again drawing upon theoretical principles, dictate that the first sign of viral rebound warrants a switch to a new batch of drugs. But what about patients who see their CD4+ remain stable or continue to increase, long after viral load rears its ugly head? Is it possible to keep these patients on their current regimen, thereby preserving future options and delaying a litany of new side effects that may come with switching?

It also seems as if the issue of structured treatment interruptions—what many of us rightfully call drug holidays—has already been written off as a potential disaster by many researchers. "Viral load increases when therapy is stopped!" bemoan some researchers. "CD4+ cell counts drop as well!" cry others. Well, of course they do. But a central question remains: Do drug holidays or, quite possibly, pulsed therapy approaches (i.e., treat when the CD4+ cell count is low and stop when it stabilizes) reduce the risk of side effects or help reverse side effects that have already occurred? Will they encourage patients to be compliant with their therapy, knowing that a break is just around the corner? More importantly, are the risks of these approaches any worse than the risks of lifelong, unrelenting therapy?

Perhaps once we put the *people* living with HIV, and not just the virus, back into research, we'll find the answers we invariably need.

Sean R. Hosein

Science and Medicine Editor at CATIE (Canadian AIDS Treatment Information Exchange), Canada's national AIDS treatment information agency, and a science advisor to the Ontario Ministry of Health's AIDS Bureau

One finding that has puzzled researchers for the past two decades is that the immune systems of people living with HIV/AIDS (PHAs) are clearly quite active; indeed, in some cases, they are apparently hyperactive. Yet these PHAs still eventually develop serious infections. It may be that HIV tricks the immune system into suppressing the activity of useful antiviral defenses while allowing ineffective responses to continue. Ultimately, this type of situation works in favor of the virus. Despite all that HIV throws at the immune system, some PHAs survive for many years without taking anti-HIV therapy and without developing symptoms of AIDS or having their cell counts fall significantly. These people are called long-term nonprogressors (LTNPs). By studying how the immune systems of LTNPs adapt to and survive HIV infection, researchers could eventually invent therapies that are more effective and that, hopefully, cause fewer side effects.

An important chemical signal (or cytokine) used by cells is interleukin-10 (IL-10). When produced in large amounts by cells, IL-10 can weaken the immune response against viruses, bacteria and fungi. Some researchers think that HIV may trick the immune system into producing large amounts of IL-10, weakening the body's ability to fight the virus. Researchers at Mt. Sinai Hospital in Toronto have been studying the immune systems of PHAs, including some LTNPs, with a focus on production of IL-10.

The Mt. Sinai researchers found that T-cells taken from LTNPs and healthy HIV negative people produced relatively low levels of IL-10. T-cells taken from people with AIDS produced between two to five times more IL-10. Those PHAs who took highly active antiretroviral therapy (HAART) were able to significantly reduce their levels of IL-10. The work done in Toronto confirms that of another research team in Norway, which also found that HAART reduced IL-10 levels but was not able to return them to low, normal levels seen in HIV negative people. An immune booster that would be able to further reduce levels of IL-10 in PHAs taking HAART might enhance the immune system's ability to fight HIV. IL-10 also appears to play a role in regulating the CD4+ cell count. Reducing levels of IL-10 could help raise the CD4+ cell count in PHAs. Expect to see more research on therapies to reduce IL-10 levels in the future.

Paul Volberding, MD

Vice Chair of Medicine at the University of California, San Francisco, Chief of the Medical Service at the San Francisco VA Medical Center

HIV care continues, in mid-2001, to benefit from the availability of several potent drug regimens. Despite limitations in convenience and toxicity, and even though many patients have accumulated increasing resistance to therapy, they are still living free of the devastating opportunistic infections, cancers and wasting illnesses that were the predictable result of infection until 1996. The striking clinical benefit of HIV therapy and the very low mortality from HIV in most parts of the US will wane somewhat over the next few years. There is good data that CD4 cell counts will eventually decline in the face of ongoing HIV replication, and there is no reason to think that "AIDS" won't again appear if one's CD4 cells remain severely depressed for prolonged times. But there is also reason for optimism. New drugs and drug classes are far enough along in development that should have less cross resistance with today's approved agents, and we may eventually learn enough about the nature of immune control of HIV infection to develop therapies that slow or even reverse the immune damage caused by HIV infection.

The next several years will, in the developed world, focus on incremental advances in dealing with resistance and in managing the side effects of current drugs, and we will see several new drugs approved. It is impossible to imagine sufficient progress in vaccines to lead to approval of any protective vaccine soon, but research in this field will be the target of substantial investment and much new knowledge will certainly follow. Our focus will continue to shift to include the developing countries where the epidemic remains uncontrolled. HIV will be an effective model and probe to see how much true commitment the developed world has to distribute the lifesaving results of a largely public investment in new treatments and vaccines for diseases easily controlled for those with adequate resources. Hopefully, we will live to see the day when all have the hope that comes with health.

For more information...

If you'd like to contact any of the writers who contributed to this issue of *CRIA Update* or to get more information about the organizations, research or advocacy projects mentioned in these commentaries, please email us at treatmented@criany.org or call us at (212) 924-3934 extension 111.

Yvette Delph

Antiviral Project Director for Treatment Action Group

In the 20 years since AIDS was first described, HIV has been identified as the causative agent, tests for HIV have been developed, three classes of antiretroviral drugs (ARDs) have been licensed, and much has been learned about the effects of HIV disease and the drugs used to treat it. Even more needs to be learned. There is still no cure. Current ARDs cause major and sometimes fatal side effects, they need to be taken for life and their effectiveness against HIV is compromised within months in many people. And an effective vaccine is a very long way off.

There is a great need for new classes of ARDs that are effective against new HIV targets. The last new class of agents to reach the market, the non-nucleoside reverse transcriptase inhibitors (NNRTIs), was first licensed in the US in June 1996. There are some new drug classes in the pipeline. Hopefully they will provide effective ways of combating HIV, especially HIV that is resistant to current ARDs. These new drug classes include:

Entry Inhibitors

Attachment inhibitors

- PRO 542
- CXCR4 co-receptor inhibitors
  - bicyclams (AMD-3100)
  - polyphemusins (T22)
- CCR5 co-receptor inhibitors
  - SC-351125
  - PRO 140
  - TAK 779
  - SCH-D

Fusion inhibitors

- T-20
- T-1249
- d-peptides
- 5-helix

Integrase Inhibitors

diketo acids

- L-708,906
- L-731,988

thiazolothiazepines

Viral Capsid Formation & Assembly Inhibitors

glycyl-prolyl-glycine amide (GPG-NH_2)

There are other potential new targets in the HIV infection and replication cycle, which also offer the hope of novel, effective drugs against HIV. These include:

- DC-SIGN inhibitors
- Uncoating inhibitors
- Maturation inhibitors
- Zinc finger inhibitors
- Inhibitors of HIV regulatory proteins
  (nef, rev, tat, vif, vpr)

Another important area of research is in the area of therapeutic drug monitoring (TDM). It is difficult to predict the blood levels of the current ARDs even when taken as prescribed and, because they are so prone to the development of both resistance and toxicity, it is postulated that adjusting drug dosages based on monitoring of drug levels may increase efficacy and decrease toxicity. Studies are underway involving TDM of protease inhibitors and NNRTIs. Initial results are conflicting but promising. TDM of nucleoside reverse transcriptase inhibitors (NRTIs) is not feasible at this time, as intracellular levels of nucleoside triphosphates would need to be measured.

Other areas of research which require greater attention and resources are: the effects of gender, ethnic, racial and age differences as well as co-morbidities (like hepatitis, diabetes, and cardiovascular disease) on HIV disease, its treatment and care. As the prevalence of multidrug resistant (MDR) HIV increases, options and strategies for salvage therapy are an increasing and urgent need. In general, pharmaceutical companies have not been willing to cooperate in studying investigational agents together in highly treatment-experienced persons. This is a disgrace that needs to be remedied urgently.

Structured intermittent therapy (SIT) is being studied for varying therapeutic strategies, including: as an immune stimulant (auto vaccination); for management of MDR; and for reduction of toxicity. SIT research deserves to be closely followed – especially as a possible way to decrease toxicity, for which it seems to hold the most promise.

There is also a great need for well-designed, systematic research into the long-term (more than five years) effectiveness and toxicity of ARDs. Questions like when to start antiretroviral therapy (ART), what to start with, and when and how to change ART remain unanswered. Effective mechanisms for detecting known as well as unknown long-term toxicities of ARDs need to be developed and implemented.

There is much that remains to be answered about HIV treatment. It is imperative that adequate resources be dedicated and, even more important, the political will mustered to address these issues with the necessary urgency.

A Long Road Traveled

(continued from page 4)

early intervention with AZT argued that HAART should be given to almost everyone with HIV. A panel dominated by these supposed experts was created by the government in 1996 to produce guidelines on using HAART, leading to a recommendation that treatment be started when the T-cell count fell below 500 or if viral load rose above 20,000 copies. The handful of community representatives involved (supported, it should be emphasized, by a few brave doctors on the panel) had to threaten a walkout in order to have the following text inserted as a footnote: "some experts would defer therapy until the CD4 count falls below 350." Earlier this year, the guidelines were revised to reflect this more cautious approach and, once again, the early intervention cheerleaders have somehow held on to their jobs and reputations.

The guesswork employed to guide initiation of therapy was echoed in recommendations for second and third line regimens aimed at people with multiple drug resistance. An unappealingly small market for industry, it was left to a small group of committed activists and doctors – the Coalition for Salvage Therapy (CST) – to beat the bushes for trials that might help guide those running out of treatment options. This uphill battle is still being fought today and, tragically, many people (including several sorely missed members of CST) have died as a consequence.

The idea that HAART may produce cumulative and unpredictable side effects was also largely ignored by many (although not all) researchers. Instead, it became popular to blame the strange syndromes being reported by the community on HIV itself. Thus, "HIV-Associated Lipodystrophy (HAL)" was christened, despite the fact that HIV had little, if anything, to do with the drug-induced syndrome of elevated blood fats and mitochondrial damage (mitochondria are vital energy-producing components of human cells). Reports by women of sex-specific toxicities also went unheeded for several years, something that might not have occurred had there been adequate representation of women in HAART trials. Treatments for these problems, and strategies for uncovering their cause and reducing their incidence, have been slow to reach clinical trials, as is evidenced by the grand total of eight listed in the most recent New York State clinical trial directory.

Yet another significant, and under-appreciated, assumption about HAART was that it had to be used continuously to produce sustained health benefits. Dr. David Ho solidified this idea by proposing that HIV might be eradicated with prolonged therapy. The shocking lack of biological plausibility did not prevent Ho's hypothesis from being embraced by large swathes of both the scientific and (perhaps more understandably and forgivably) HIV/AIDS advocacy communities. It took the increasing burden of treatment fatigue and toxicity to give pause to eradication enthusiasts, and the real world perspectives of clinicians like Bill Powderly to eventually note that perhaps treatment interruptions could be both safe and beneficial if a careful eye was kept on immune system function and health.

"The shocking lack of biological plausibility did not prevent [the eradication] hypothesis from being embraced..."

Percolating around the issue of interrupting treatment was a radical claim made by immunologist Bruce Walker at the 1998 International AIDS Conference in Geneva: "Eradication is not required – the immune system can control HIV." Although supported by considerable evidence from animal studies – and some hints from humans – the notion was greeted with skepticism and, in some cases, outright disdain. The lack of interest on the part of the pharmaceutical industry is perhaps not surprising, given that the emphasis was reducing time on drug therapy. However, like the broadening of opportunistic infection studies in the early '90's, activism by many groups has helped force the issue. Get a copy of CRIA's latest clinical trials directory for New York State, and you'll see the first few multi-site studies of both treatment interruptions and interruptions accompanied by therapeutic immunizations that might conceivably enhance control of HIV in the absence of HAART. Even large companies like Merck and GlaxoSmithKline are now exploring these strategies in studies, making this an area to watch closely as research moves into the new millennium.

Eyes on the Prize (2001-?)

The disheartening persistence of agendas that ill serve people with HIV/AIDS cannot undo the successes of the post-HAART epoch. The number of deaths and AIDS diagnoses has plummeted in the wealthier nations of the world, providing some respite from the horror of the epidemic's early years. But as the mainstream media reflect on two decades of AIDS, it is disturbing to read quotes that so selectively portray the effects of community activism and exaggerate the role of leaders who have so often let down people with HIV. Anthony Fauci, who has kept his job as director of NIAID, credits advocates for making clinical trials "user friendly," but chooses not to mention the PCP prevention trial that CRI pulled off when no one else would. The pharmaceutical industry lauds the accelerated approval mechanisms that have hurried drugs to market, but cannot seem to conduct post-marketing studies to identify new side effects or define how the drugs should best be used. Robert Schooley, who once described a colleague as "imbecilic" for advocating delayed initiation of HAART, still runs the ACTG. While sobering, these facts serve as a reminder that continuing activism and community involvement in HIV/AIDS research is essential if the oft-forgotten, but surely ultimate, goal is to be reached. A cure.

Richard Jefferys, formerly Access Project Director at the AIDS Treatment Data Network, now writes for the IAVI (International AIDS Vaccine Initiative) Report.

Roy Gulick, MD, MPH

Associate Professor of Medicine, Weill Medical College of Cornell University, Director, Cornell Clinical Trials Unit

The goal of clinical research is to use laboratory discoveries to develop and perform studies in human subjects with the hope of defining new and better treatment strategies for a disease or illness. HIV clinical researchers first tested combinations of drugs that have reduced HIV-related illness and death dramatically over the last five years. Despite this success, clinical studies remain critical for continued advancements in several important areas:

- **new drugs** continue to be needed for patients who have exhausted all available treatment options or who cannot tolerate the current drugs; examples are drugs with new ways of working, such as the HIV entry inhibitors T-1249 and AMD-3100, and the HIV integrase inhibitor, S-1360;

- **immune boosters**, such as HIV vaccines, need to be tested to supplement the current anti-HIV drugs; one example are the new HIV DNA therapeutic vaccines to be tested in patients doing well on their current HIV combination regimens;

- **simplification** of current treatments will promote better adherence and a better quality of life for patients while maintaining strong antiviral activity; examples include comparing current HIV treatment combinations to a single pill that contains three separate drugs given twice a day or newer once-a-day treatment regimens;

- **side effect treatments** and strategies are important to try to reduce both acute and longer-term complications associated with the therapies; one example are drugs that lower levels of lipids (blood fats);

- **hepatitis C** treatments need to be improved and tested in patients who are co-infected with HIV and the hepatitis C virus; examples include the use of combination therapies of interferon and ribavrin and the use of additional novel strategies such as pre-treatment with interleukin-2 (T cell growth factor).

One of the effects of the significant progress we have made in HIV treatment is that healthcare providers and HIV-infected individuals may be less inclined to think of research studies as an option. To ensure continued progress in the field, we must continue to support participation in HIV clinical research efforts.

Claire Rappoport, MA

Community Representative, Community Programs on Clinical Research on AIDS (CPCRA) and Person with AIDS

For most people, the news of a positive HIV test, while emotionally challenging, is no longer an emergency. The basic state of managing this disease should be about striking a balance between drug effectiveness and side effect management. What I see emphasized in the future of AIDS research is the refinement of treatment strategies and monitoring, adjunctive treatments, and drug development.

Currently, I see more emphasis being placed on understanding how we can better sequence HAART drugs and incorporate new drug treatments looming on the horizon. The HAART medications are very powerful, and differences in patients' absorption levels and side effects often occur. There is still much to learn about how we use these drugs in terms of sequencing, dosing, pulsing/treatment interruptions, etc. Similar to the current use of resistance testing, the use of therapeutic drug monitoring and other future monitoring tests will become more prevalent. The hope is to tailor each treatment regimen for each specific patient.

While the debate of whether HIV is a chronic manageable disease is still open, this change in view has opened the door for treatments that are promising with regard to immune strengthening and modulating. Examples are drugs like the interleukins coupled with an emphasis on basic health maintenance and nutrition. I see this trend continuing.

I see that many drug companies are losing interest in developing treatments for AIDS. Additionally, the furor over the development of side effects and their management has discouraged some patients and health care providers from as aggressively seeking them out - although ultimately, I think that most HIV infected folks will take some of these powerful medications at some point in their lives. Having said that, there are second and third generation antiretroviral drugs on the horizon, and I am sure that these will be prescribed and used widely once they are available. I think the key, again, will be to balance their effectiveness with the potential side effects.

In terms of what I would like to see, I hope that both therapeutic and preventative vaccine development and testing continues. I also hope that manufacturers of these drugs explore alternative delivery methods to make compliance much easier. Wouldn't it be great to wear a patch that could deliver continuous medication and only change it once a month?

Paul Simmons Director of treatment information and advocacy at The Center for AIDS in Houston

What's up with AIDS research? The same thing that's up with my hair - thinning.

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the trade association for the pharmaceutical industry, 23 agents are under investigation for HIV infection. Five of them are "me too" drugs that add nothing important to the therapeutic arsenal, and another three have suspended development. Of the remaining 15, only eight are potentially novel or second generation agents, and some of them may not withstand further study.

In part, the success of combination treatment generally, and of the protease inhibitors specifically, has undermined our once potent sense of urgency to find new drugs for treating HIV. Since Americans with AIDS are no longer dropping like British cattle, we've grown complacent. But that's only half the story.

The damaging effect of some of our activism has created an environment hostile to new investment in HIV drug discovery. Nowadays we activists have taken to demanding that free-market pharmaceutical companies behave like social service agencies and give their products away at cost – or less. The drug companies, we say, "have blood on their hands;" they are "killing people with AIDS;" they are making "obscene profits." Our rhetoric is belligerent, even hysterical, and it is not without consequence.

Don't misunderstand me. The drug companies *are* out for money. In pursuit of the dollar, they sometimes misrepresent data, buy off our doctors, and exploit people. But those same companies – through risk-taking fueled by the allure of profit – also save lives, *including yours and mine.*

Except for long-term non-progressors and a few others, we adults in the U.S. living with HIV today are in a fix of our own making. When I seroconverted in 1996, I wasn't the victim of Ronald Reagan or Merck or the military industrial complex. I was the victim of my own inexplicable stupidity. No, I didn't want HIV, nor did I deserve it. Whatever any of us did to contract the virus, we don't merit a death sentence. But only through tortured logic could I now demand that pharmaceutical shareholders rescue me – at their expense – from the consequences of my own choices.

"We see ourselves in high archetypical battle with the evil capitalists, and we revel in the emotional satisfaction of moral arrogance."

If you agree that the poor both at home and abroad should have the life-saving power of antiretroviral therapy, I say bully for you. But talk to our government, which is, by the way, the largest purchaser of anti-HIV drugs. The government, and not private industry, is responsible for public policy. And talk also to the governments in Africa, many of which are so corrupt and inefficient that they can't control dysentery much less HIV. (To this day, South Africa has yet to declare the HIV epidemic a national emergency.) But it makes about as much sense to insist that drug companies not profit from our disease as it would to insist that the farmer not profit from our hunger.

And yet, the steady assault on for-profit drug research is likely to continue, and grow even shriller. Reason is often subordinate to emotion. Sometimes the actual consequences of an idea don't matter to us. What matters are the good intentions that inform our ideas and the good feelings we get from them. We see ourselves in high archetypical battle with the evil capitalists, and we revel in the emotional satisfaction of moral arrogance.

Unfortunately, you may be the one to pay for our conceit. Industry will offer an ever-shrinking arsenal of new anti-HIV drugs, as it turns its attention to other, less troublesome areas. As one company executive said, "We can make just as much money doing other things and with a lot less hassle." We activists are haranguing the industry out of AIDS research.

A few years from now, your anti-HIV drugs will exhaust their benefit. But instead of finding something new to help you, industry will busy itself developing the next round of treatment for small breasts and impotence. If it's any comfort, as you lay in a hospital bed with tubes coming from every orifice, we activists will organize an angry demonstration on the sidewalk below. But there will be no new HIV treatment for us to demand, only free breast enlargements and free erections.

Taking the Pulse *(from page 1)*

When we look at the direction of AIDS research overall, it's important to acknowledge how much progress we have made. As often as it's said, we need to say it again: many people are living longer and better than they did before antiretroviral chemotherapy. AIDS wards in this country are no longer overflowing with dying patients. Great progress has been made. But HIV infection rates are rising again. We have not learned how to prevent infection, either by effectively helping people to change risky behaviors or by developing effective microbicides or vaccines. Many people are learning that they're co-infected with HIV and hepatitis C, developing cirrhosis and dying waiting for liver transplants. And there are severe limitations to currently available drug regimens. Resistance to antiretroviral drugs is increasing and many of our friends, clients and patients are running out of treatment options. Side effects are also reducing the effectiveness of these wonder drugs. Different people are developing immune system damage at different rates, revealing interesting and important individual characteristics that affect disease progression.

Julie Davids

Director of the Critical Path AIDS Project, member of ACT UP Philadelphia, co-founder of Project TEACH, and member of the Health GAP Coalition, which fights for global HIV treatment access

With mounting toxicities and treatment fatigue in the US and Europe, we may be in the hangover phase of antiviral cocktails, but many still depend on the hair of the dog that bit them to stay healthy until we have a better answer.

The growing movement for global treatment access is also searching for safer, lower cost HAART options. The needs of people with HIV around the world overlap when it comes to treatment strategies that do not mandate lifelong chemotherapy.

At the 2001 Retrovirus Conference, NIAID presented data on a handful of people who alternated seven days on, seven days off their combo for almost a year – without viral breakthrough or resistance. This study design represents an acknowledgement that people can't take pills day in, day out for a lifetime – and that treatment interruptions, even without boosting immune response, could make life more livable and treatment more affordable if they can be done without viral rebound. Half the cost of drugs! Half the time on treatment! Current plans are to expand the study to include more people, and try different lengths of treatment and breaks.

Research advocates and access activists must join together to get answers on who can delay HAART, and whether those who need treatment can safely use less drugs, less of the time, less times a day and/or with less pills. To do so, we must confront drug company threats that seek to divide us. An increasingly common trope is that the fight for global drug access will undercut drug company efforts to find better therapies and The Cure. If we continue to challenge industry to lower prices or allow generic competition in hard-hit and cash-strapped nations, industry threatens to "leave AIDS" in search of the next hard-on pill.

Some people point to the trickling drug development pipeline as validation of this threat, with few truly novel approaches winding their way towards market. It's a pretty scary situation for those running out of treatment options. But this is a troubling phenomenon we've been tracking for years. The pipeline was showing signs of serious dehydration at least four years ago, two years before the all-too-real and decades-long AIDS horror in Africa and elsewhere hit the front page of the New York Times.

"It is the solidarity of people worldwide that will keep the heat on for the cure."

If we look at the cold hard economics, the greatest potential impact on the bottom line of AIDS Pharma right now is the change in the US treatment guidelines, which finally recognize the lack of data – and plethora of toxicities and side effects – for starting treatment early in folks without symptoms or low CD4 counts. Clearly, this represents a drastically reduced market in the cash cow regions – and don't even talk about treatment interruptions.

People with AIDS and other activists fought for research on AIDS medications. And we may need to fight to keep the research going, rather then letting the focus drift to more profitable areas. It is the solidarity of people worldwide that will keep the heat on for the cure.

The industry has no reason to disclose that they may be disinvesting from AIDS due to more sensible, data-based guidelines, when they can instead pit activists against activists and blame the fight for global drug access – just as they have blamed women and their advocates for the past 15 years. We have heard similar arguments against prioritizing research in women with HIV. We have been told that the development of drugs for all is dependent on refusing to direct resources to crucial questions about side effects, toxicities, markers and drug levels in women. Yet many answers could come from small Phase I trials, new models of statistical analysis and data collection, or lab analysis of stored samples. "It costs too much to study women," insists the industry that has raised US drug prices 10% a year for the past two years.

We help ourselves and our loved ones in the United States when we act in solidarity with the tens of millions across the world without access to treatment. It is the promise of medication that has finally driven home that the world must deal with AIDS and spotlighted the absolute necessity of vaccine development.

The pressing need for drastically simplified – but equally effective – treatment across the world has stimulated interest to find strategies that could help make life easier here at home.

We face urgent health policy challenges as well, including equitable access to drugs and medical care, the advent of managed care and its effects on clinical practices, and the adequacy and distribution of research funds. For complicated reasons, the advances in HIV treatment have yet to benefit huge numbers of people in our inner cities and rural areas. The diminishing rate of private donations to AIDS research is a disturbing sign that much of the public – because of naïveté, willful ignorance or worse – now views the disease as chronic, manageable and, therefore, less important.

And, while one may take comfort from the tremendous progress that has been made in this country and the western world, the increasingly apparent ravages HIV is inflicting on the developing world are being addressed far too slowly. Without a vaccine, without significant resources being invested now for the provision of treatment and medical care in the developing world, without a tide of western medical professionals making their skills and knowledge available to help care for the sick in Africa and Asia, without a global Marshall plan for HIV and AIDS, we ain't seen nothing yet.

Jack Killen, MD

Director, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health

The XIII International AIDS Conference, held last July in Durban, South Africa, marked a sea change in attitudes and beliefs about treatment of HIV-infected people in the developing world. A remarkable cascade of events, unimaginable even a year ago, is now unfolding. There have been dramatic declines in drug prices, public and private sector agencies are mobilizing to plan and implement pilot care programs, and governments are making real financial commitments. These efforts are tremendously exciting and deserve vigorous and universal support.

While well-intended, the public focus on drug prices has obscured the real barriers to care for people with HIV in the developing world – severely inadequate health care systems and infrastructure, and too few trained people to work in them. In other words, even if drug pricing was not an issue in the hardest hit developing countries, the health care systems are not there to deliver them.

The following anecdote is illustrative. In March, I visited a small rural health center in Uganda, near the Tanzanian border. It was staffed by a nurse/health officer and a midwife. We asked the midwife what she does when she has a difficult delivery. She told us that she sends the woman to the regional hospital, located about 20 kilometers down a muddy, rutted, dirt road. Transportation, when she has gasoline, is by motor scooter; if not, by bicycle. (I was told that 70% of the population of Uganda live more than ten kilometers from such a health facility). We also visited the regional hospital. I counted at least 80 people waiting to see one of the three staff physicians; children shared beds and adults slept on the floor or outside; the laboratory staff used alcohol lamps, manual blood counting equipment, and a hand-cranked centrifuge to spin down blood. In the bigger picture, it is vital to remember that a top health priority of the country is ensuring clean water for the entire population; it is a little more than half-way there.

This is the context – and it is the rule, not the exception – in which medical care in the developing world must be delivered. The appalling inequality of health care around the world is tragic and not in any way unique to HIV/AIDS (though there are certainly many unique HIV/AIDS problems). Nonetheless, it is the enormity of the chasm between here and there which explains why so little has been done for care of people with HIV infection in the developing world. These are daunting obstacles which must be overcome.

"The appalling inequality of health care around the world is tragic and not in any way unique to HIV/AIDS."

Any formula aimed at making even a dent in the problem of HIV care in the developing world must include the following:

1) capacity to provide basic health care must be built, not just for people with HIV disease, but for all;

2) ongoing HIV prevention programs must be preserved, expanded, and integrated with care initiatives;

3) research attempting to identify sustainable care in developing world settings must be initiated;

4) in-country research capability, both human and infrastructure, must be built;

5) the genuine moral dilemmas behind many significant ethical problems must be evaluated with care and reason. Tactically, unprecedented levels of public and private collaboration and cooperation must be brought to bear, since it will be essential to leverage resources from various sectors and countries. It will also be necessary to take the long view, aiming toward incremental steps forward through pilot programs and innovative approaches to treatment.

Jill Cadman

Long-time HIV treatment advocate and educator, currently editing the PositiveWords.com HIV Newsletter website

Scientific research has brought us to where we are today in our understanding of so many diseases. HIV research in particular seems to have progressed both amazingly fast and agonizingly slow at the same time. We have come so far, but have lost so many along the way. In haste, we have sometimes jumped to wrong conclusions, and there are those who have suffered by following approaches that were considered the standard of care at the time, but have since been discredited or revised. Also, despite regulations and controls, clinical trial results are subject to misinterpretation and bias and must be evaluated with a critical eye.

Having said this, thousands of people are alive and well because of the hard work and dedication of researchers. HIV-positive women have been able to have healthy children and can look forward to seeing them grow up. Many significant questions have been answered and numerous important drugs and diagnostic tests are available to the public in economies that can afford

them. But in many ways, the hard work has only just begun. The really tough areas, like salvage therapy, prevention and vaccine research, are lagging behind.

At this point in time, those who are newly diagnosed or stable have many options, albeit with a high cost to pay in terms of side effects. While I would like to see more progress in the area of side effect management (both alternative and mainstream) and the development of less toxic new drugs or combinations of drugs, I feel that people who have run through all the antiviral drugs should be addressed first. Those in need of salvage therapy are basically back to the pre-AZT era. They have no treatment options left and are vulnerable to opportunistic infections. Creative approaches to salvage therapy must receive more of a concerted effort.

The other priority has to be in the area of prevention. There is such a strong link between substance use and HIV infection that behavioral research into addiction prevention and control is very important. Finally, true behavior change is so difficult that I think the most important goal has to be a preventative vaccine to stop infection in the first place.

If we have learned one thing in the twenty years of this epidemic, it is that HIV highlights hidden or ignored generic social problems and points the way to their resolution. We must not be overcome by the enormity of the challenge ahead, but use the current situation as a leverage point to bring about change in the quality of all health care for those in the developing world. It is long, long overdue.

Donna Tinnerello MS, RD, CD/N

Cabrini Medical Center

In 1997 we first observed a phenomenon in HIV positive patients treated with HAART (highly active antiretroviral therapy). They called it lipodystrophy syndrome and it consists of abnormal body fat distribution – fat loss in the arms, legs, buttocks and facial area, and excess fat deposition in the abdomen, back of the neck (buffalo hump) and breast tissue. The syndrome includes the metabolic abnormalities of hyperlipidemia, insulin resistance and diabetes. In the past two years, bone demineralization – osteopenia and more advanced osteoporosis – has been described in patients on HAART.

What role does the virus play and how much of it is drug related? If it is drug related what drugs are to blame? Is it age-related? As people live longer is it more likely? What are the long-term ramifications? Why are some populations less susceptible than others?

"What role does the virus play [in lipodystrophy] and how much of it is drug related?"

We never really saw any of this until there was HAART or did we? According to Dr. Don Kotler at St. Luke's-Roosevelt, if we look back to the days of monotherapy (e.g. AZT), there were patients walking around in pants held up by suspenders; they had abdominal fat, but no fat in the buttocks. We always had lipid abnormalities – untreated patients had very high serum triglycerides, but they also had very low serum cholesterol and HDL cholesterol. We never checked bone density. The life expectancy was predictable in the majority of untreated people with AIDS.

It seems that none of the three classes of drugs are blame-free and that changing regimens will not necessarily cause reversal of the syndrome. According to Kotler, body composition and metabolic changes, once established, may include a self-promoting feature that prevents resolution.

We obviously do not want people living with HIV to not take medications or to stop taking them. Dying from an AIDS-related illness is a far worse fate than the fatty changes and risk of heart disease. What are the treatment options? What can nutrition and medicine do to lessen these side effects?

Large scale research on nutrition, exercise and the syndrome would help sort out how much is diet related and what can be accomplished by changing the aspects of care that can be controlled and self managed. So far the only pharmaceutical anabolic agent that seems to have any effect on reducing body fat is Serostim (growth hormone). More research in the area of anabolics might also be in order.

John S. James

Editor and Publisher of AIDS Treatment News

Could a seeming glitch in HIV vaccine progress also be key to getting vaccines to Africa and elsewhere much faster than expected?

Some of the new experimental vaccines do not prevent infection, but may instead greatly lower viral load, preventing or much reducing both illness and transmission. It appears that such "non-sterilizing" vaccines could be tested much faster than those which prevent infection -- by comparing viral loads of persons infected after receiving the vaccine, vs. those infected after receiving the placebo. Probably the first few dozen infections (in both groups combined) would be more than enough for statistical proof -- regardless of the total N (number of people) in the trial (which probably would still be large, but only to show the needed infections sooner). The difference is that with a non-sterilizing vaccine, you can see how well it works in particular individuals. And the inevitable random fluctuation and resulting unbalance in the size of the infected/vaccine vs. infected/placebo groups does not bias the result of the trial -- while this fluctuation does bias the result in a conventional vaccine trial, requiring a larger and longer trial to compensate.

Such a phase III trial might prove a vaccine works within a year or two. Yes, the proven efficacy would then be short term. But even short-term efficacy alone might justify use of the vaccine in epidemic areas, because it would at least reduce transmission (especially during the very infectious primary illness). And later failure of the vaccine would show up quickly in viral load comparisons -- and in case it did, boosters could be tested in the same trial, and proven rapidly in the same way, probably ahead of need in the field (where people would have been vaccinated later).

If it's true that non-sterilizing vaccines can be tested much faster than vaccines which prevent infection, the public-health opportunities need immediate attention.

In another area, most but not all researchers have given up on antibodies for helping to control HIV. Clearly, most antibodies produced in response to HIV are not effective. But immunologists are now finding some antibodies that do work – which may provide a way to rationally design an antibody component of a vaccine (or possibly a treatment). Researchers could quickly screen these vaccines in small trials, to make sure they do indeed produce the antibodies which had been shown effective in laboratory, animal, or human tests.

"If it's true that non-sterilizing vaccines can be tested much faster than vaccines which prevent infection, the public-health opportunities need immediate attention."

In other immune-based research, a big problem is standardization of laboratory tests. Immunologists have shown interesting results for many years, but often their work is not followed up because it's hard to compare data from different laboratories. There isn't much commercial incentive as long as the only market is research projects, which often want to develop their own tests anyway. And individual researchers are seldom interested in standardizing tests. NIAID has experience in this area, and we should make sure there are no funding or other avoidable obstacles preventing it from doing this work.

In other areas, pathogenesis research may be able to identify new targets in the development of infection, or of disease – possibly resulting in new classes of drugs.

As for existing antiretrovirals, we need more research and medical attention to the possibility that safe nutritional or other treatments could help prevent or relieve some of the side effects. Unfortunately this hasn't been a glamorous area. And while pharmaceutical companies have done some research on the causes of drug toxicities, the bottom line is that they make their big money on spin, so they have incentive to avoid raising the public profile of the problems with their drugs. Perhaps the community will have to take the lead in this area – organizing and applying what's already known, pointing out key strategic research projects, and making sure they get done.

Community Forums

CRIA co-sponsors monthly educational forums on AIDS research and treatment issues.

Wednesday, September 19th
Immune-based Therapies

Wednesday, October 17th
Pregnancy and HIV

Wednesday, November 14th
Body Shape Changes: Weight Loss & Fat Redistribution

Forums are held at 7pm in the Cronin Auditorium, 10th floor of St. Vincent's Hospital at 11th St. and 7th Ave., Manhattan. Summaries of past forums are available on CRIA's website: www.criany.org.

CRIA at NATAF 2001

CRIA is a co-sponsor of NATAF 2001 (North American AIDS Treatment Action Forum), which takes place December 2-5 in Vancouver. This conference, sponsored by the National Minority AIDS Council (NMAC), provides treatment advocates, activists, educators and people living with HIV the opportunity to broaden their knowledge of HIV treatment issues, build advocacy skills, and develop strategies to advocate for people living with HIV/AIDS within their communities, nationally and internationally. A limited number of scholarships to NATAF 2001 are available. To register for the conference, to apply for a scholarship, or for more information, visit the NMAC website (www.nmac.org) or call CRIA at (212) 924-3934 extension 120 and we'll send you a brochure.

New Staff Introductions

CRIA is pleased to welcome Noemi Olivo, MSN/Epidemiology as Associate Director of Research. Ms. Olivo joined our staff in April to direct the day-to-day operations of the clinic research staff as we undertake a substantial growth in CRIA's scientific agenda. She comes to us with a 20-year career in developing and conducting HIV behavioral, clinical research, and epidemiological protocols for the State of New Mexico, the University of Arizona, and the Centers for Disease Control and Prevention. Most recently, she was the Project Director at Visible Genetics, Inc. for their major Vigilance II study, of which CRIA is a super site. We are grateful that Ms. Olivo will now be making her contribution to AIDS research through the private non-profit sector at CRIA.

Mark Milano is CRIA's new Publications Manager. Prior to joining our agency, Mark was the Coordinator of Experimental Treatment Information at the New York State Department of Health AIDS Institute, where he managed the production of several significant HIV/AIDS publications for both consumer and medical provider audiences. At CRIA, he will be overseeing the production of our new publication, *HIV/AIDS Clinical Trials: A Directory for New York State*, as well as *CRIA Update* and our topic-specific HIV treatment education brochures. Mark comes to us with experience as a treatment educator as well, so he'll conduct group workshops and staff trainings at agencies throughout New York City.

Quality of Life Survey

Our Winter 2000/2001 issue of *CRIA Update* included a quality of life survey, designed with the help of Bruce D. Rapkin, Ph.D. of Memorial Sloan-Kettering Cancer Center in New York. We appreciate the time that so many people took to complete the survey – we received over one hundred responses. Thanks also to The Body for posting the survey on their website, which allowed readers to complete it electronically. Your responses have been entered into a statistical database, and Dr. Rapkin is currently analyzing the data. We look forward to his summary, which will be published in the next issue of *CRIA Update*.

CRIA Becomes ACRIA

CRIA has assumed a "doing business as" (DBA) name – AIDS Community Research Initiative of America, or ACRIA. We've created this new name for participation in the Combined Federal Campaign (CFC), a major annual fundraising appeal to government workers. CRIA has been in the CFC for four years now, with less than stellar results. Experts in this fundraising appeal have told us that the primary reason our revenues are falling short is that donors looking to support an AIDS charity are unable to find our agency in the CFC guide, and that our name gives the impression that we only impact a small area of the U.S. Donors are also much more likely to choose charities with AIDS as the first word in their name simply because they come across them earlier in the CFC guide. Many other charities have adopted DBAs to clarify their mission and promote fundraising. We've chosen ACRIA because it not only conveys the national scope of our current programmatic activities but also retains very close approximation to CRIA and will be identifiable as the same agency. So if you see ACRIA, be assured it's us only operating under our DBA name.

Special thanks to:

HIV InSite

at the University of California, San Francisco for their assistance in identifying trial sites and gathering data for CRIA's HIV/AIDS clinical trials directory.

Visit their website at:

hivinsite.uscf.edu

for extensive information on HIV/AIDS clinical trials and treatment.

acknowledging our friends...

GENEROUS CONTRIBUTORS

The following persons, corporations and organizations made major donations between April 1, 2001 and June 15, 2001 to support CRIA's research and education efforts:

Will Barnet
Estate of Al Blois
Bristol Myers Squibb Company
Broadway Cares/
Equity Fights AIDS Inc.
Charles Cowles Gallery
Karin Davie
Federated Department Stores
Foundation
Erik Hanson
Gale Hayman &
William Haseltine MD
The Howard Gilman Foundation
Robert A. Landau
Lillet
Roche Laboratories
Kenny Scharf
Serono Laboratories, Inc.
Hunt Slonem
Billy Sullivan
Juergen Teller
The Verizon Foundation
Vanessa von Bismarck
Randy Wray
Lisa Yuskavage

Thoughtful donations in memory of the following remind us of what is at stake in the fight against AIDS:

Barbara Frey
Tom Larivey
Chet Pannell
Oswaldo Perez
Dr. Jeffrey Wallach

Contributions in support of CRIA's vital research initiatives were made in honor of the following individuals:

David Meador
Michael Rohrs & Tom Rosato
William Toarmina

COMMUNITY RESEARCH INITIATIVE ON AIDS

230 West 38th Street, 7th floor, New York, NY 10018
Phone: (212) 924-3934, Fax (212) 924-3936

NON-PROFIT ORG.
U.S. POSTAGE PAID
New York, NY
Permit No. 4732

Change Service Requested

***CRIA Update* is sponsored in part by unrestricted educational grants from:**